Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Association between vaccination against COVID-19 and postmenopausal bleeding

OBJECTIVE: Postmenopausal bleeding (PMB) following vaccination against COVID-19 has been reported anecdotally and may influence attitudes toward vaccination, but formal studies are lacking.[1–3] We therefore evaluated whether vaccination was associated with an increase in diagnosis of postmenopausal bleeding in a large, diverse, community-based cohort of women.

STUDY DESIGN: Following approval by the Kaiser Permanente Northern California Institutional Review Board, we identified female patients aged ≥55 years at the time of COVID-19 vaccination between December 1, 2020 and May 31, 2021, excluding those with a history of hysterectomy or without continuous health plan membership for at least 12 months before and 8 months following vaccination. Incident PMB was identified by abnormal bleeding diagnosis codes (N95.0, N93.0, N93.8, N93.9) assigned at an outpatient emergency department or video or telephone visit among women who did not have a previous PMB diagnosis for at least 12 months. A self-controlled risk interval methodology was used,[4] comparing the incidence of PMB during 3 consecutive 16-week "risk intervals": 1 interval before vaccination (Interval 0) and 2 intervals following vaccination (Intervals 1 and 2), with incidence assessed as the number of incident diagnoses occurring during that interval divided by the population at risk for incident bleeding. Patient histories documented at diagnosis were manually reviewed for 250 patients in each interval to estimate the proportion who had delayed presentation for ≥2 months from the onset of bleeding.

RESULTS: Among 485,644 women meeting inclusion criteria, 47% were of non-White race with a median age of 67 years (range, 55–105), with 95.4% receiving a messenger RNA (mRNA) vaccine: 52.4% received BNT162b2 (Pfizer–BioNTech, New York, NY) and 43% received mRNA-1273 (Moderna, Cambridge, MA). During the prevaccination interval (Interval 0), the incidence of PMB was 0.39% (95% confidence interval [CI], 0.38–0.41), increasing slightly after vaccination to 0.47% during Interval 1 (95% CI, 0.45–0.49), and then decreasing to 0.43% (95% CI, 0.41–0.45) during Interval 2 (2-sided Cochran–Armitage test for linear trend in proportions; P=.004), (Table). The proportion of women whose diagnosis of PMB was delayed ≥2 months from the date of onset of bleeding was similar across the 3 consecutive time intervals (23.6%, 22.8%, and 20.4%, respectively; P=.39).

CONCLUSION: In a large, diverse community cohort, vaccination against COVID-19 was associated with a slight increase in the rate of PMB, as assessed by clinical diagnoses, which did not seem to be attributable to delays in presentation. However, in absolute numbers, the observed increase represents <1 in 1000 additional women diagnosed with bleeding after vaccination compared with before vaccination. Among premenopausal women, COVID-19 vaccination was reported to be associated with a <1 day increase in menstrual cycle length but no change in menses length.[5] Although the mechanisms underlying premenopausal and postmenopausal bleeding are expected to be distinct, our study similarly found that vaccination was associated with a change in bleeding that was statistically significant but of a magnitude

TABLE
Incidence of postmenopausal bleeding before and after vaccination

	Prevaccination interval 0 (16 wk)	Postvaccination interval 1 (1–16 wk)	Postvaccination interval 2 (17–34 wk)	*P* value for trend[a]	Fisher exact test *P* value with adjustments for multiple comparisons[b]
Women at risk of incident bleeding (N)	485,132	484,971	484,572		
Incident PMB diagnoses[c]	1914	2265	2099		
Incidence of PMB	0.39% (0.38–0.41)	0.47% (0.45–0.49)	0.43% (0.41–0.45)	.004	Pre vs Post 1, P<.001 Pre vs Post 2, P=.012 Post 1 vs Post 2, P=.051 Pre vs (Post 1+Post 2), P<.001

PMB, postmenopausal bleeding.

[a] Cochran–Armitage test for linear trend in proportions, 2-tailed *P* value; [b] The Bonferroni method was used for *P* value adjustment for multiple comparisons; [c] Incident cases defined by diagnosis of PMB among women without a previous diagnosis of PMB during the preceding 12 months.

Suh-Burgmann. Association between vaccination against COVID-19 and postmenopausal bleeding. Am J Obstet Gynecol 2022.

so small that the clinical impact at the population level is negligible. The findings provide reassurance that COVID-19 vaccination is not associated with a clinically meaningful increase in the incidence of postmenopausal bleeding. ■

Elizabeth J. Suh-Burgmann, MD
Division of Gynecologic Oncology
The Permanente Medical Group
1425 S. Main St.
Walnut Creek, CA 94596
Betty.Suh-Burgmann@kp.org

Cassidy Tierney, MD
Department of Obstetrics and Gynecology
Kaiser Permanente Oakland Medical Center
Oakland, CA

Yun-Yi Hung, PhD
Julie A. Schmittdiel, PhD
Division of Research
Kaiser Permanente Northern California
Oakland, CA

The authors report no conflict of interest.

The study was funded by The Permanente Medical Group Physician Researcher Program.

REFERENCES

1. Male V. Menstrual changes after covid-19 vaccination. BMJ 2021;374:n2211.
2. Royal College of Obstetricians and Gynaecologists. RCOG/FSRH respond to reports of 30,000 women's periods affected after COVID-19 vaccine. 2021. Available at: https://www.rcog.org.uk/news/rcogfsrh-respond-to-reports-of-30-000-women-s-periods-affected-after-covid-19-vaccine/. Accessed May 1, 2022.
3. Centers for Disease Control and Prevention. Selected adverse events reported after COVID-19 vaccination. 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html. Accessed May 1, 2022.
4. McClure DL, Glanz JM, Xu S, Hambidge SJ, Mullooly JP, Baggs J. Comparison of epidemiologic methods for active surveillance of vaccine safety. Vaccine 2008;26:3341–5.
5. Edelman A, Boniface ER, Benhar E, et al. Association between menstrual cycle length and coronavirus disease 2019 (COVID-19) vaccination: a U.S. cohort. Obstet Gynecol 2022;139:481–9.

 https://doi.org/10.1016/j.ajog.2022.07.006

Gaps in evidence-based medicine: underrepresented populations still excluded from research trials following 2018 recommendations from the Health and Human Services Task Force on Research Specific to Pregnant Women and Lactating Women

OBJECTIVE: Despite being at higher risk for COVID-19–related complications, pregnant and lactating women were excluded from the initial trials leading to Emergency Use Authorizations for COVID-19 vaccinations.[1] These exclusions came 2 years after the United States Department of Health and Human Services (HHS) Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) provided recommendations to Congress and HHS on how to increase inclusion of traditionally excluded groups in research.[2]

Lack of randomized controlled trials including pregnant and lactating patients limits clinicians' ability to make evidence-based recommendations. The explicit exclusion of these groups from trials means that clinicians must rely on less sound data, often from observational studies or expert opinions, when making recommendations. Although these exclusions are framed as protective, they result in a lack of evidence-based care and harm patients as effects, dosing changes, and metabolic changes are not studied. Patients in other commonly excluded groups are exposed to the same harms, with limited evidence available to steer decision-making for patients with disabilities, the elderly, and children. This study aimed to determine if National Institutes of Health (NIH)–funded trials were more likely to include underrepresented groups after the 2018 PRGLAC recommendations.

STUDY DESIGN: All actively recruiting NIH-funded phase 3 and 4 trials were downloaded from ClinicalTrials.gov on January 7, 2022. These trials were reviewed for inclusion criteria and population of interest. Data collected from this date were then compared with data published before these recommendations.[3]

RESULTS: Of 419 actively recruiting trials, explicit exclusion was noted in 69% for pregnant individuals, 50% for lactating women, 81% for children, 23% for older adults, and 15% for individuals with disabilities. In comparison with